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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,228	02/28/2006	Paul Stoffels	TIP-0058-USPCT	7472
27777	7590	05/12/2009	EXAMINER	
PHILIP S. JOHNSON JOHNSON & JOHNSON ONE JOHNSON & JOHNSON PLAZA NEW BRUNSWICK, NJ 08933-7003			RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1614	
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			05/12/2009	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/570,228	<b>Applicant(s)</b> STOFFELS, PAUL	
	<b>Examiner</b> SAVITHA RAO	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 12 February 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,6,19-21 and 24-29 is/are pending in the application.
- 4a) Of the above claim(s) 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6, 19-21 and 25-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 1,6, 19-21 and 24-29 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 02/12/2009 is acknowledged. Claims 1 is amended and new claims 25-29 are added. Instant claim 24 is withdrawn from consideration as being drawn to a non-elected invention. Claims under consideration in the instant office action are claims 1,6, 19-21 and 25-29

Applicants' arguments, filed 02/12/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### ***Claim Rejections - 35 USC § 112***

#### ***(New matter rejection)***

**This rejection is necessitated by the newly submitted claims filed on 10/17/2008**

The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply

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with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. claim 26 recites "the combination of drugs TMC278, tenofovir and emtricitabine each in separate pharmaceutically acceptable carriers" in the 2<sup>nd</sup> and last line of the claim and instant claim 28 recites "the combination where in TMC278, tenofovir and emtricitabine are together in a single pharmaceutically acceptable carrier " in the 2<sup>nd</sup> and last line of the claim. Although the disclosure recites the drugs being in a pharmaceutically acceptable carrier on page 4- lines 31-32, page 15-line 24-25, lines 26-27 and line 35-36, page 16- lines 4-5, 12-13 and 20-21 and in pages 17 and 21. nowhere in the disclosure is the combination where in the three drugs are provides in separate pharmaceutically acceptable carriers or in a single pharmaceutically acceptable carriers is recited.

Accordingly, claim 26 and 28 are properly rejected under 35 U.S.C. 112 for new matter addition in the claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

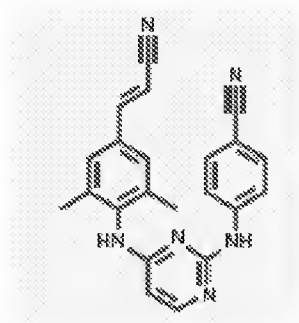
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1,6, 19-21 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guillemont (WO 03/016306, referenced in the instant IDS) in view of Peiperl et al (Viread, drug overview, August 2003) and Hazen et al (Journal of AIDS, 32, pp 255-258, 2003) as evidenced by Clercq (Il Farmaco 54 (1999) 26-45)

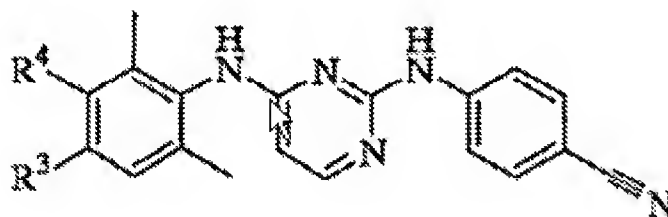
Instant application claims a combination comprising TMC278 (NNRTI) or a stereoisomeric form thereof with a nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir.

TMC278 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with the following structure:

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Guillemont teaches the E and the Z-isomeric forms of TMC278 as compounds 1 and 10 on pages 91 and 95 of the instant disclosure respectively (see below)



Comp No.	Ex. No.	R <sup>3</sup>	R <sup>4</sup>	Physical data mp, °C / (MH <sup>+</sup> )*
1	B1/B6a	-CH=CH-CN	H	mp. 245, (E)
10	B6a	-CH=CH-CN	H	mp. 258°C (Z)

Guillemont additionally discloses these compounds to display antiretroviral properties (page 43, lines 4-5) and as active against (multi) drug resistant HIV strains, especially HIV strains that have acquired resistance to one or more art-known non-nucleoside reverse transcriptase inhibitors (page 43, lines 2029). Guillemont additionally teaches that compounds of his invention may be used alone or in combination with other therapeutic agents such as anti-viral, antibiotics etc (page 51,

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lines 12-15). Guillemont also teaches that the exact doses and frequency of administration depends on the particular compound, the severity of condition being treated, the age, weight and general physical condition of the particular patient as well as other medications the individual may be taking and is well known to those skilled in the art (page 51, lines 1-6). Guillemont teaches that his compounds of his invention may be formulated into various pharmaceutical forms for administration purposes in combination with pharmaceutically acceptable carriers (page 44, lines 26-33).

Guillemont additionally teaches that the combination of an antiretroviral compound and the compound of formula (I) (which encompasses compound 1 and 10 shown above) can be used in medicine. (Page 51, line 25 to page 52, line 13). Guillemont exemplifies nucleosides reverse transcriptase inhibitors (NRTI) such as ziduvudine, lamivudine and stavudine which can be used in combination with the compounds of formula I (page 51, lines 34-35) and in addition Guillemont exemplifies other NtRTI's such as tenofovir to be used in combination with the inventive compound (page 52, line 12).

Guillemont further teaches the combination to be administered simultaneously, separate or sequentially for use in anti-HIV treatment and also teaches that the different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers (page 52, lines 27-30). Guillemont additionally teaches that by administering compounds of his invention with other anti-viral agents which target different events in the viral life-cycle, the therapeutic effect of these compounds can be potentiated and combination therapies exert synergistic effect, may reduce the dosage of a given conventional anti-retroviral agent, may reduce or eliminate the side effects of

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conventional single anti-retroviral therapy and may increase the efficacy of the conventional agent without increasing associated toxicity (page 52, lines 15-17). Finally Guillemont teaches his compositions to be formulated as tablets, capsules, parenteral compositions, (page 45, and lines 1-26).

Clercq is used here as evidentiary document to support the use of NNRTI and NtRTI drugs in HIV 1 therapy. Clercq teaches perspective of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 Infection (title). Clercq teaches that NNRTI resistance mutations is generally felt as compromising the clinical utility of the NNRTI's (page 29, right col. last paragraph to page 30 left col. 1st paragraph). Clercq further teaches that the mutually antagonistic effects of different resistance mutations and the hypersensitivity that is seen under some conditions argue in favor of the combined use of NNRTI's with NRTI (nucleoside/nucleotide reverse transcriptase inhibitors). Additionally, Clercq teaches that while achieving synergism in their anti-HIV action, different drugs combined may also reduce the risk of HIV drug resistance development and diminish toxic side effects. (Page 30, right col., 1st paragraph to page 31, right col., 1st paragraph). Clercq additionally teaches that the compound should be administered concomitantly (page 31, right col., 1st paragraph).

Guillemont does not teach the specific utility of the combination of the three drugs MC278, Tenofovir and emtricitabine together in HIV treatment and does not teach once a day dosing of the combination

However, Peiperl teaches that tenofovir which is an adenosine nucleotide analogue was approved by the FDA in 2001 for use in combination with other



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antiretroviral agents in adults with HIV infection (page 1, under approval). Peiperl additionally teaches that tenofovir in combination with lamivudine (nucleoside reverse transcriptase inhibitor) and efavirenz (non-nucleoside reverse transcriptase inhibitor) was found to be well tolerated and apparently more potent than the standard regimen (page 2, 1st paragraph) and in a clinical comparison this combination was associated with a lower rate of toxicities attributable to mitochondrial dysfunction (page 3, 1st paragraph). Peiperl additionally teaches that tenofovir is available in tablet form with once daily dosing (page 1). As such it would be obvious to one of ordinary skill in the art to develop combination therapy involving the three different anti-HIV drugs for once a day dosing format.

With regards to the ratio limitation in instant claim 19 wherein the applicant claims a weight ratio of each couple of components to be in the range from 1/4 to 4/1 the references above do not teach the exact ratio in a combination of the NNRTI, NRTI and NtRTI inhibitors. However, it would be within the skill of an ordinary artisan to be able to titrate the dosage of both compounds in a composition to obtain the desired pharmacological and pharmaceutical effects. The ratio also will depend on the dosage regimen if it is sequential or concomitant administration. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to instant claim 21 and 25, combining the three drugs instantly claimed into a pharmaceutical composition or kit would have been obvious to one of

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ordinary skill in the art at the time of invention, since all the three drugs are known to be used in the treatment of HIV infections and the three broad categories of the drugs have been shown to be used in combination together.

With regards to instant claim 26, Guillemont's teachings of using the combination as sequential or separate use indicates that each of the drugs were in separate pharmaceutical carriers and as such would have been obvious to an ordinarily skilled artisan to formulate each in separate carriers.

With regards to providing information to a patient,. It is inherently clear that any kit comprising a drug or administration of a drug comprises information addressing any possible adverse effects associated with the drug. It appears to be merely implicit that information addressing the adverse effects of drugs and its usage is provided along with the medication. Accordingly one of ordinary skill in the art will be obligated to provide the consumers of their product with all the information necessary to ensure that the products are used appropriately and pose no danger to the health and safety of the user. In addition, Examiner would like to draw applicants attention to MPEP section 2112.01, section III which states: Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).

In view of the foregoing references, the instantly claimed combination comprising TMC278 ,tenofovir and emtricitabine would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Guillemont teaches both

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isoforms of TMC278 and suggest combination of that with Tenofovir or lamivudine for use as a medicine for HIV 1 treatment. Emtricitabine is a functional equivalent of lamivudine as taught by Hazen et al. who teaches that emtricitabine is a nucleoside reverse transcriptase inhibitor similar to lamivudine with antiviral activity against HIV-1. Hazen additionally teaches that both compounds share a common pathway through 2'-deoxycytidine kinase for conversion to their active nucleoside triphosphates (page 255, right col., 1<sup>st</sup> paragraph)

Clerc and Peiperl's teachings further provide motivation to an ordinarily skilled artisan to combine the three different categories (NNRTI, NtRTI and NRTI ) of anti HIV drugs to treat HIV infections. . All three references provide one of ordinary skill in the art motivation to combine a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a Nucleotide reverse transcriptase inhibitor (NtRTI) and a nucleoside reverse transcriptase inhibitor (NRTI) and the advantages of using them in combination. All of the materials instantly claimed were known in the art to be useful to obtain an efficient anti HIV-1 drug. Accordingly, the references above provide motivation to one of ordinary skill in the art to formulate a medicine comprising the combination of the compounds taught by Guillemont which includes the two isomeric forms of TMC278 tenofovir, and emtricitabine for HIV 1 treatment. Moreover, NNRTIs, NtRTIs and NTRTI are individually known in the art as agents for treating HIV-1 conditions as shown supra, whose efficacy when administered alone is well established. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very

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same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that three individually known anti-HIV agents would, when combined, provide a third composition also useful for treating HIV flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to rebut this natural presumption. Further, it is clear from the prior art that NNRTI combination with other drugs such as NtRTIs or NRTI's provide several advantages such as synergistic effect, reduction in the dosage and reduction of side effects. One skilled in the art would have been imbued with at least a reasonable expectation that a combination of NNRTI with NtRTI and NRTII would provide a composition with enhanced and beneficial effects.

**Response to applicant's arguments filed on February 12<sup>th</sup> 2009:**

In light of the new grounds of rejection above, the arguments submitted on 02/12/2009 which was for the previously submitted rejection is moot.

***Conclusion***

**Claims 1,6, 19-21 and 25-29 are rejected. No claims are allowed**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614